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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/028,395	02/24/98	PROCKOP	D 9598-32

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EXAMINER	
KERR, J	
ART UNIT	**PAPER NUMBER**
1633	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/028,395	Prockop et al.
Examiner	**Group Art Unit**
Janet M. Kerr	1633

☒ Responsive to communication(s) filed on *Feb 14, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-20* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5, 11*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

Applicants' amendment, filed on 2/14/00, has been entered.

Claims 1-20 remain pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record and the reasons below.

The claims are directed to methods of treating a human patient having a disease, disorder or condition of the central nervous system (CNS) comprising obtaining a bone marrow sample from a human donor, isolating stromal cells from the bone marrow and administering the isolated stromal cells to the CNS of the human patient. The disease, disorder, or condition can be a genetic defect disease, a tumor, i.e., a brain tumor, trauma, stroke, or injury to the tissues or cells of the CNS. The cells can be transfected with an isolated nucleic acid encoding a therapeutic protein, which can be a cytokine, a chemokine or a neurotrophin. The nucleic acid can be a wild type copy of a mutated, non-functioning or under-expressed gene. The isolated stromal cells can be immunologically isolated.

As stated in the office action of 10/4/99, the specification is non-enabling for the claimed methods as the specification does not provide sufficient guidance as to how one of ordinary skill in the art would treat a human patient having a disease, disorder, or condition of the CNS by administering isolated stromal cells from a human donor. The specification does not disclose any

specific disease, disorder, or condition of the central nervous system which has been subjected to the claim-designated treatment regimen, nor does the specification teach any specific methodology associated with such a treatment regimen including the number of cells to be administered for each disease, disorder, or condition, the route of administration for each disease, disorder, or condition, or the relevant cell therapy target site for the specific disease, disorder, or condition of the CNS. Nor does the specification disclose how to immunologically isolate the cells to treat a specific disease, disorder, or condition of the CNS. Moreover, as stated in the office action of 10/4/99, the state of the art at the time of filing teaches that mesenchymal stem cell transplantation and *in vivo* therapeutic effectiveness is neither routine nor predictable.

Applicant's arguments filed 2/14/00 have been fully considered but they are not persuasive. Applicants argue that the claimed cell and gene therapy methods are enabled by the specification as there has been extensive reduction to practice in the specification, that the instant application only omits that which is well-known to those skilled in the art and known to the public, and further, that it would not require undue experimentation to use the invention as claimed. Applicants rely on sections 21604.01 and 2164.02 of the MPEP to support applicants' arguments (see pages 3-4 of applicants' Response).

Applicants' arguments are not persuasive. While reduction to practice and working examples are not required in a specification, sufficient guidance and objective evidence to render the invention predictable is required. As stated in the MPEP section 2164.03:

"The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher , 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is

known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.

The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability."

In the instant case, applicants' claims are directed to a method of treating a CNS disorder by administering MSCs containing a gene encoding a therapeutic protein. The specification broadly discloses different diseases, conditions, and disorders which can be treated by cell therapy, and broadly discloses *ex vivo* gene therapy strategies for treating the diseases, conditions, or disorders of the CNS. The specification does not disclose any correlation between a specific CNS disease, condition, or disorder, and a particular method of treating the specific disease, condition, or disorder including the number of MSCs to be administered, the mode of administration of the MSCs, or the therapeutic protein required in treating the particular disease, disorder, or condition such that efficacious treatment can be attained.

As discussed in the office action of 10/4/99, cell and gene therapy are unpredictable arts. Prockop (Science, 276:71-74, 1997) indicates that several different strategies are being pursued for therapeutic use of MSCs, and that a phase I clinical trial demonstrated that the systemic infusion of autologous MSCs appears to be well tolerated, but also notes that "Obviously, however, a number of fundamental questions about MSCs still need to be resolved before they can be used for safe and effective cell and gene therapy." (see page 74, middle column). While applicants argue that reliance upon this reference is improper as it is not "prior art" (see pages 6-7 of applicants' Response), it should be noted that consideration of post-filing references is appropriate when determining whether a specification is enabling. See MPEP 2164.05(a) which states:

"In general, the examiner should not use post - filing date references to demonstrate that the patent is non - enabling. Exceptions to this rule could occur if a later - dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. In re Hogan , 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. (emphasis added) < In In re Wright ,>999 F.2d 1557, 1562,<27 USPQ2d 1510>, 1513 - 14< (Fed. Cir. 1993) an article published 5 years after the filing date of the application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms. Claims not directed to the specific virus and the specific animal were held nonenabled."

Clearly, the author of the reference, Prockop, who is also a co-inventor of the instant application, recognizes that utilization of MSCs in cell and gene therapy is neither routine nor predictable.

With respect to the reference of Gerson (Nature Medicine, 5:262-264, 1999), applicants argue that the disclosed invention overcomes or addresses the variety of issues raised with respect to the utilization of MSCs in therapeutic regimens. In particular, applicants argue that the data in the instant specification demonstrate that donor MSCs implanted in the recipient brain were found in multiple areas of the brain and behaved similarly to implanted astrocytes, and also demonstrate that the MSCs ceased synthesis of type I collagen after integration into brain tissue. Applicants also assert that Gerson's reference to Horwitz *et al.*, which discloses treatment of patients suffering from osteogenesis imperfecta (OI) by administration of MSCs also supports the successful use of MSCs to treat a disease (see pages 7-8 of applicants' Response). With regard to the Horwitz *et al.* reference, applicants arguments are not persuasive as the etiology of OI is well documented, i.e., the pathophysiology of OI is known to be correlated with mutations in the COL1A gene; such mutations are known to effect the synthesis and secretion of collagen, resulting in abnormal collagen structure, which ultimately impacts on bone architecture, bone function, and bone fragility. OI, however, is not a central nervous disease, and successful

treatment of OI by administering MSCs containing a normal collagen gene is not predictive of successful treatment of a generically claimed CNS disorder by administering MSCs containing a generically claimed therapeutic protein. The data of the instant application upon which applicants rely in support of the argument that the claims are enabled in fact support the unpredictability of utilizing MSCs in treatment regimens. For example, while the Horwitz *et al.* reference discloses that MSCs which have targeted to bone secrete normal collagen and ameliorate the pathophysiology of OI bone, applicants' data demonstrate that collagen synthesis ceases in MSCs that are targeted to the brain, and in fact, appear to differentiate into a different lineage, i.e., astrocytes. One of skill in the art would not have been able to determine a priori whether MSCs containing a therapeutic protein would in fact continue to synthesize said protein under different environmental conditions.

With regard to the Sanberg reference, applicants argue that the instant invention overcomes the issues addressed by Sanberg in that the MSCs in the instant invention would not initiate an immune response as the MSCs can be readily obtained from a syngeneic donor or from the patient being treated, or the MSCs can be immunologically isolated by using diffusion chambers. Moreover, in response to the teaching of Sanberg *et al.* that cell transplantation for treating diseases or conditions in which neurons die, such as stroke or Huntington's Disease is difficult as these disorders involve multiple neuron populations and extensive cell death throughout the brain, applicants argue that the data in the specification demonstrate that the MSCs introduced into the brain migrate and localize throughout the brain making MSCs ideal for treatment of diseases involving various areas of the brain (see pages 8-9 of applicants' Response). However these arguments are not persuasive as the specification has not provided guidance as to which CNS disease could be suitably treated with MSCs containing an appropriate therapeutic gene. While Sanberg et al state that "transplantation has a place in our arsenal of therapeutic treatments for neural degenerative diseases and stroke...", Sanberg et al also note "The potential for this line of research to eventually be used in the clinic as therapeutic treatments for degenerative diseases is becoming even more likely as development is facilitated by industrial

funding.". Thus, while transplantation appears to be a potential mode of treatment, the specific methodologies and clinical efficacy of such therapies with regard to treating central nervous system diseases remain to be established.

With regard to the Sabate reference, applicants argue that the instant invention overcomes the issues of treating CNS disorders using fetal tissue as disclosed by Sabate. Applicants assert that using MSCs obviates any ethical and technical hurdles involved in using fetal-derived cells. Moreover, applicants argue that Sabate discloses numerous gene products where the mutation, non-functional or underexpressed gene mediates a CNS disease, disorder or condition. Applicants argue that the MSCs expressing a gene of interest can be introduced directly into the CNS where the cells migrate and integrate. Applicants argue that the gene products which mediate various disease conditions of the CNS are known in the art and such teachings of that which is well-known in the art has been properly omitted from the specification. This is not persuasive as the specification only discloses the retroviral constructs pCMV-lacZ, pCOL1-lac Z, and pCOL2-lacZ which have been used to transfect the isolated stem cells (see page 7, and Example 1). The specification does not teach a correlation between an effective treatment regimen and a condition, disease, or disorder of the CNS with the administration of MSCs transfected with the retroviral constructs. Similarly, the specification does not provide guidance as to which nucleic acid sequences are suitable for encoding any and all therapeutic proteins. Although claims 10 and 13 limit the therapeutic protein to a cytokine, chemokine, or neurotrophin, the specification does not provide information with regard to the source of nucleic acids which encode the cytokine, chemokine, or neurotrophin, or the identity of a cytokine, chemokine, or neurotrophin which would have therapeutic effectiveness as a result of administration of the MSCs. In addition, the specification only broadly teaches possible promoter/regulatory sequences which can be used to direct expression of the nucleic acid encoding a therapeutic protein in a transfected MSC (see page 23). Moreover, there is no teaching in the specification as to the effect of transfecting the isolated stem cells, or the effect of the expressed therapeutic protein, on the phenotypic characteristics of the isolated stem cells, i.e.,

there is no teaching in the specification that the transfected cells would maintain morphologic and phenotypic characteristics which are required in the therapeutic effectiveness of the transfected cell population.

Applicants rely on the post-filing reference of Schwartz *et al.* which demonstrates the rat and human MSCs transduced with retroviruses encoding two therapeutic proteins express the proteins and have a therapeutic impact in a rat model of Parkinson's disease. Applicants argue that the reference of Schwartz *et al.* is representative of the level of skill in the art and demonstrates that the skilled artisan, armed with the teachings of the instant invention, would be able to practice the invention commensurate with the scope of the claims without undue experimentation (see pages 11-12 of applicants' Response). Applicants' argument is not persuasive as one demonstration of the use of MSCs encoding a particular protein associated with a particular disease model is not representative of the level of skill in the art, nor is it predictive of successful use of MSCs transfected or transduced with any and all proteins to treat any and all central nervous system diseases or disorders. There are a myriad of CNS disorders in which the etiologies are unknown or are a result of several different mechanisms. The skilled artisan would not be able to practice the invention commensurate with the scope of the claims without undue experimentation as the specification, as filed, has not provided sufficient guidance to treat all diseases or disorders of the central nervous system, nor is the art of treating CNS disorders or diseases, at the time of filing, routine and predictable. One of skill in the art would not be able to practice the invention giving the limited teachings in the specification, the lack of working examples, and the state of the art at the time of filing.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pereira *et al.* (Proc. Natl. Acad. Sci. USA, 92:4857-4861, 1995), taken with Friedmann (TIG, 10:210-214, 1994), and Caplan (J. Orthopaedic Research, 9:641-650, 1991, newly applied).

Pereira *et al.* disclose the repopulation of tissue, including brain tissue, by adherent marrow cells intravenously administered to irradiated mice, and suggest that the adherent marrow cells serve as long-term precursor cells for these tissue (see Table 1, and pages 4859-4860, under "Discussion").

While Pereira *et al.* disclose *in vivo* differentiation of adherent marrow cells to resulting in a phenotype which is the same as that of the differentiated cells in the brain tissue, Pereira *et al.* do not disclose *in vitro* differentiation of adherent marrow cells resulting in the same differentiated cell type as that present in the culture with the adherent marrow cells. However, Caplan teaches that the progression from stem cell to final end phenotype is marked by discrete stages with transit from one stage to the next dependent on local cuing from surrounding cells as well as signals emitted by the cell itself and the reception of its own signaling; that the sum of these various intrinsic and extrinsic signals defines the developmental position of the cells; and further that this methodology to determine "positional information has been experimentally approached in *in vitro* investigations in the study of other cell types which have the potential to

differentiate into various phenotypes (see page 641, right column). In addition, Friedmann discloses that mammalian CNS contains some cellular elements that are probably derived from the bone marrow, such as microglia (see page 212, left column, first paragraph).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to co-culture isolated stem cells with a population of differentiated cells, such as astrocytes to establish if the differentiated cell type alone is sufficient to provide the necessary cues to guide differentiation of the marrow-derived cells, or if the entire tissue microenvironment is required to provide the cues necessary for differentiation of the marrow-derived cells. One of ordinary skill would have been motivated to utilize such a method to determine the environmental conditions, such as growth factor requirements, cell-cell interactions between stem cells and differentiated cells, or extracellular matrix normally associated with the *in vivo* environment, that are required to direct the differentiation of marrow-derived cells into other cells types, such as astrocytes, in view of the teachings of Caplan that the progression from stem cell to final end phenotype is marked by discrete stages with transit from one stage to the next dependent on local cuing from surrounding cells as well as signals emitted by the cell itself and the reception of its own signaling; that the sum of these various intrinsic and extrinsic signals defines the developmental position of the cells; and further that this methodology to determine "positional information has been experimentally approached in *in vitro* investigations in the study of other cell types which have the potential to differentiate into various phenotypes (see page 641, right column). In view of the teachings of Friedmann that marrow contains cells which can be directed to differentiate into central nervous system-associated cell types, and the disclosure of Pereira *et al.* that administration of marrow-derived cells results in the differentiation of the marrow-derived cells into different lineages depending on which tissue is repopulated, one of ordinary skill in the art would have been motivated to establish cell culture conditions which allow the identification of bone marrow-derived cells, and which allow the identification of the microenvironment required to recapitulate the *in vivo* observations of and Pereira *et al.* Moreover, one of ordinary skill of the art would have had a high expectation of successfully establishing the *in vitro* conditions

which are permissive for directing the differentiation of marrow-derived cells into specific cell lineages, such as astrocytes, as this methodology has been previously used to establish paracrine and autocrine regulation of cells which can differentiate into various phenotypes as taught by Caplan.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Applicant's arguments filed 2/14/00 have been fully considered but they are not persuasive. Applicants argue that the references relied upon do not teach or suggest all of the claim limitations. Applicants argue that Pereira and Friedmann do not disclose *in vitro* co-culturing of mesenchymal stem cells with a differentiated cell type, nor do the references disclose that stromal cell differentiation can be directed and accomplished in cell culture (see pages 31-34 of applicants' Response).

These arguments are not persuasive. The references relied upon disclose that mesenchymal stem cells are capable of differentiating into specific cell types, including cell types associated with the central nervous system, and that the differentiation of the cells is based on the microenvironment of the cells. In view of the teachings of Caplan that differentiation of cells into specific phenotypes is dependent upon paracrine and autocrine signaling, it would have been obvious and well within the purview to co-culture an isolated stromal cell with a differentiated cell type to establish the paracrine and autocrine signaling mechanisms which direct an undifferentiated cell to a particular differentiated phenotype.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to John LeGuyader, Supervisory Primary Examiner of Art Unit 1633, at (703) 308-0447. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

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DEBORAH J. CLARK
PATENT EXAMINER